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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,274	10/09/2007	Rehab Al-Jamal	MUR-06-1101	9435

35811 7590 12/03/2008

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
12/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,274	AL-JAMAL ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/22/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *5-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/3/08* _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-18 are pending.

Upon reconsideration the Examiner has rejoined Group I and II.

2. Applicant's election without traverse of Group II, claims 1, 3-4 and 15-16 (now claims 1-4 and 15-16), drawn to a method of promoting tissue repair comprising the step of administering a compound which modulates the function of beta 1 integrin to a tissue in need of repair, wherein the compound modulates apoptosis filed on 9/22/08, is acknowledged.

3. Claims 5-14 and 17-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 1-4 and 15-16 are under examination as they read on a method of promoting tissue repair comprising the step of administering a compound which modulates the function of beta 1 integrin to a tissue in need of repair, wherein the compound modulates apoptosis.

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

6. Applicant's IDS, filed 1/3/08, is acknowledged.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 16 is indefinite in the recitation of "JB1a" because its characteristics are not known. The use of "JB1a" monoclonal antibody as the sole means of identifying the claimed antibody and hybridoma renders the claim indefinite because "JB1a" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct hybridoma or cell line. For Example the art recognizes the same antibody as JB10.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 16 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma that produce the JB1a antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

It is noted in the specification on page 26 at lines 19-22, discloses that functional modifying antibody of β1integrin obtainable as produced by a commercial clone JB1a from Chemicon (this antibody may also be known as J10). However, the Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. A product could be commercially available but only at a price that effectively eliminates accessibility to those desiring to obtain a sample. The relationship between the applicant relying on a biological material and the commercial supplier is one factor that would be considered in determining whether the biological material was known and readily available. However, the mere fact that the biological material is commercially available only through the patent holder or the patent holder's agents or assigns shall not, by itself, justify a finding that the necessary material is not readily available, absent reason to believe that access to the biological material would later be improperly restricted.

11. Claims 1-4 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of promoting tissue repair in lung emphysema comprising administering the monoclonal antibody produced by commercial clone JB1a (once the deposit issue is satisfied).

Applicant is not in possession of a method of promoting any “tissue repair” comprising the step of administering any “compound which modulates the function of beta 1 integrin" to a tissue in need of repair in claim 1, wherein the “compound modulates the metalloproteinase (MMP) balance” in claim 2, or "the compound modulated apoptosis” in claim 3, wherein the modulation of the apoptotic activity has a resultant modulation in the metalloproteinase (MMP) balance in claim 4, wherein the compound is an antibody in claim 15, wherein the antibody is a monoclonal antibody produced by commercial clone JB1a in claim 16.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (compound which modulates the function of beta 1 integrin, compound modulates the MMP balance, compound modulates apoptosis) to describe the claimed genus, nor does it provide a description of structural features that are common to species (compound which modulates the function of beta 1 integrin, compound modulates the MMP balance, compound modulates apoptosis). The specification provides no structural description of such compounds other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed compounds looks like. The specification's disclosure is inadequate to describe the claimed genus of compounds.

Applicant has disclosed only JB1a antibody would promote tissue repair in lung emphysema; therefore, the skilled artisan cannot envision all the contemplated compound possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. Claims 1-4 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting tissue repair in lung emphysema comprising administering the monoclonal antibody produced by commercial clone JB1a (once

the deposit issue is satisfied), does not reasonably provide enablement for a method of promoting any "tissue repair" comprising the step of administering any "compound which modulates the function of beta 1 integrin" to a tissue in need of repair in claim 1, wherein the "compound modulates the metalloproteinase (MMP) balance" in claim 2, or "the compound modulated apoptosis" in claim 3, wherein the modulation of the apoptotic activity has a resultant modulation in the metalloproteinase (MMP) balance in claim 4, wherein the compound is an antibody in claim 15, wherein the antibody is a monoclonal antibody produced by commercial clone JB1a in claim 16. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only a single monoclonal antibody produced by commercial clone JB1a which binds to a site of amino acid residues 82 to 87 of the mature beta 1 integrin (see abstract) in the promotion of tissue repair of lung emphysema. The instant claims encompass in their breadth *any* compound which "modulates the function of beta 1 integrin", "modulates the MMP balance"; or "modulates apoptosis", including those that comprise the "modulation of the apoptotic activity has a resultant modulation in the MMP balance"; or a compound that is an antibody to β1 integrin to "promote tissue repair".

The specification on page 49, lines 4-10 discloses that when administered [JB1a] to animals which have emphysematous lungs, the treatment reversed the abnormal increase in the mean linear intercept (LM) as an index of air space enlargement, lung size and abnormal lung function as well as signs of inflammation. Furthermore, there was a decrease in cell death.

The functional activities of the claimed "compound" in claims 1-4 are mutually exclusive in that they reach opposing endpoints, and in that they employ structurally distinct *agonists* or *antagonists* to accomplish these mutually exclusive endpoints. The term "modulates" indicates both inhibiting and stimulating. The skilled artisan would not have a reasonable expectation that the same compound that would *inhibit* the function of beta 1 integrin, MMP balance and apoptosis, would also serve to *enhance* the function of beta 1 integrin, MMP balance and apoptosis. Consequently the skilled artisan would not know how to use the instant invention as broadly claimed. Further, there is insufficient biochemical or structural information to enable the skilled artisan to make and use the "compound", as broadly claimed. "It is not sufficient to

define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). The specification fails to demonstrate the effect of the claimed compounds on tissue repair. Moreover, the skilled in the art would not know what activity applicant is claiming. The claim does not contemplate a specific activity.

At issue is whether or not the claimed compounds, which modulate the function of β1 integrin would function to promote tissue repair. However, in order for this therapy to be predictable, β1 integrin modulation must play a role in all tissue repairs. However, Grose et al (IDS reference AR) in Development 129:2303-2315 (2002) teach that their results reveal a strongly impaired migratory capacity of β1-deficient Keratinocytes in vitro and a dramatic delay in epithelial migration during wound repair in K5β1-null mice. Grose et al present the first in vivo evidence in support of findings from in vitro studies that have shown β1 integrins to be key players in cell migration. However, their results also demonstrate that keratinocytes are not totally dependent on this integrin subunit to heal their wounds. Rather, other integrins appear to compensate at least partially for the lack of β1, leading to complete, although imperfect, re-epithelialisation (page 2314, last ¶). Grose et al teach that keratinocytes proliferation rate in the β1 null keratinocytes was not reduced in early wounds and even increased in late wounds (abstract). Importantly, Grose et al teach that β1-deficient epidermis did cover the wound bed, but the epithelial architecture was abnormal. Zweers et al in J. Invest. Dermatol. 127:467-479, 2007, teaches that integrin α2β1 is required for regulation of murine wound angiogenesis but is dispensable for reepithelialization. Zweers et al teach that reepithelialization of excisional wounds of α2β1-null mice was not impaired, indicating that keratinocytes do not require adhesion to or migration on collagen for wound closure (see abstract). Applicant has no working examples demonstrating an *in vivo* treatment regiment with anti-β1 antibodies to promote any tissue repair, and the state of the art taught the "β1-deficient animals", α2β1 integrin, is dispensable for reepithelialization. Further, the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed method for promoting tissue repair using anti-β1 antibodies with a reasonable expectation of success. One skill in the art would concluded that a strategy of administering ant-β1 antibody in dermal tissue would require further understanding of the role of anti-β1 in re-epithelializtion.

Further, at issue the antibody of claim 15 which modulates the function of beta 1 integrin. The specification on page 47, line 16-29 discloses that functional modification of β1 integrin through a domain corresponding to amino acid residues 82 to 87 and to a lesser extent through a domain not yet specifically identified, but thought to be in the EFG-like repeat domain distinct from the 82 to 87 domain, induces a substantial time- and dose-dependent increase in ECM in a human lung epithelial cell line (NCI-H441) in monolayer and human lung explants as well as human lung derived culture in monolayer or co-culture system. The response was observed using two different antibodies against β1 integrin though the magnitude of the response was variable. These domains are different from those previously described which bind to the amino acid sequence residues 207 to 218. It is also distinct from the known stimulatory domains which are localized

to those amino acid residues and residues 657 to 670 and 671 to 703. Modulation of the cytokine TGF-β induced a less profound increase which was also time- and dose-dependent. Further, the specification discloses that the functional modifying antibody of β1 integrin, JB1a was added to the cultures. The b1 integrin stimulatory antibody TS2/16 was also added to demonstrate the specificity of the JB1a action. The β1 integrin inhibitory antibody 6S6 was also added (page 52, lines 1-8). Figs 15 and 16 of the instant specification demonstrated that the anti-β1 integrin antibody TS2/16, which binds the 207-218 amino acid sequence, and 6S6 clone, which binds a discontinuous unmapped epitope, had no effect on proteoglycans or MMP9. Accordingly, besides the JB1a antibody, the skilled in the art would not know what compound/anti-β1 antibody would modulate the function of beta 1 integrin can be used in the claimed method of promoting tissue repair.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 1-4 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Leu et al (JBC, 278(36):33801-33808, Sept. 2003, of record).

Leu et al teach a method of promoting tissue repair comprising the step of contacting CCN 1 which modulates the function of beta 1 integrin in angiogenesis (wound healing) (see abstract and page 33801, 2nd col., top ¶) as claimed in claim 1. Leu et al demonstrate that human skin fibroblasts adhere specifically to the T1 sequence (GQKCIVQTTSWSQCSKS) within domain III of CCN 1, and this process is blocked by anti-β1 monoclonal antibodies (see abstract).

Claim 15 is included because the prior art administered anti-β1 monoclonal antibodies. It is the examiner's position that identical compounds (anti-β1 integrin antibodies) cannot have mutually exclusive functions.

While the prior art teachings may be silent as to the peptide/antibody "modulates the MMP balance", "modulates apoptosis" "wherein the modulation of the apoptotic activity has a resultant modulation in the MMP balance" per se; the method, the product used in the reference method are the same as the claimed method. Therefore, these claimed limitations are considered inherent properties of the referenced compounds.

The reference teachings anticipate the claimed invention.

14. Claim 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al (JBC 278(26):24200-24208, June 2003 of record).

Lin et al teach that CCN3 induces neovascularization when implanted in rat cornea, demonstrating that it is a novel angiogenic inducer. Lin et al concluded that these findings show that CCN3 is a ligand of integrins α5β1, acts directly upon endothelial cells to stimulate pro-angiogenic activities, and induces angiogenesis in vivo (see abstract) as claimed in claim 1.

While the prior art teachings may be silent as to the peptide/antibody "modulates the MMP balance", "modulates apoptosis" "wherein the modulation of the apoptotic activity has a resultant modulation in the MMP balance" per se; the method, the product used in the reference method are the same as the claimed method. Therefore, these claimed limitations are considered inherent properties of the referenced compounds.

The reference teachings anticipate the claimed invention.

14. Claim 1-4 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by US. Pat. No. 6,251,419.

The `419 patent claims the use of a membrane system for the controlled tissue regeneration of the periodontium, comprising a resorbable polymer membrane, said membrane comprising: (a) a first antibody which binds to an integrin α6 subunit; and (b) a second antibody, which binds to an integrin β1 subunit (see patented claims 1, 11, 13-14 and 16 in particular). The `419 patent teaches that in epithelial wound healing, particularly the integrin subunits α6 and β-1 serve for connecting the keratocytes migrating into the wound region with all extracellular matrix proteins of the basal membrane. The invention is now based on the fact that growth inhibition of the epithelium and growth stimulation shall simultaneously take place in the connective tissue. This serves for supporting regeneration of the functional periodontium and accelerated wound healing (see col., 2 lines 26-32 in particular).

The term "comprising" in base claim 1 is open-ended. It would open up the claim to include the extra polymer membrane and anti-α6 antibodies. Further, the `419 patent uses only anti-β1 antibodies in group III under the example (col., 3).

While the prior art teachings may be silent as to the peptide/antibody "modulates the MMP balance", "modulates apoptosis" "wherein the modulation of the apoptotic activity has a resultant modulation in the MMP balance" per se; the method, the product used in the reference method are the same as the claimed method. Therefore, these claimed limitations are considered inherent properties of the referenced compounds.

The reference teachings anticipate the claimed invention.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 30, 2008

/Maher M. Haddad/
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